AD_____

Award Number: DAMD17-01-1-0782

TITLE: Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome

PRINCIPAL INVESTIGATOR: Pamela Dalton, Ph.D.

CONTRACTING ORGANIZATION: Baylor College of Medicine
Houston, Texas 77030

REPORT DATE: September 2004

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 2004	Annual (1 Sep 2003 - 31 Aug 2004)

4. TITLE AND SUBTITLE
Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome

5. FUNDING NUMBERS
DAMD17-01-1-0782

6. AUTHOR(S)

Pamela Dalton, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Monell Chemical Senses Center
Philadelphia, PA 19104-3308

E-Mail: pdalton@pobox.upenn.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

Troops deployed in the Persian Gulf War were exposed to an unusually diverse mix of odorous chemicals at the same time as they were exposed to physiological and psychological stressors B a scenario that research in animal models suggests will lead to the development of specific conditioned responses. The goal of this research is to investigate the extent to which people can acquire stress reactions as conditioned responses to odors and exhibit health symptoms as a result of such conditioning episodes. Thus, the paradigm investigated in this project can serve as a model system for examining and understanding the persistent symptom constellations found in GWS and other stress-mediated syndromes. Results from the first three studies strongly suggest that odor-stress conditioning can mediate elevations in hormonal status (salivary cortisol) self-reported stress, health symptoms and judged cognitive effort on memory tests, and that cognitive information about the nature of the chemical odor may enhance the stress and health symptom reports over that which is due to conditioning alone. Current studies are continuing to explore additional parameters of the odor-stress conditioning paradigm.

14. SUBJECT TERMS
odors, conditioning, stress

15. NUMBER OF PAGES
30

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

INTRODUCTION:

The overall goal of this project is to investigate the hypothesis that the symptom constellation of Gulf War Syndrome (GWS) and other stress-mediated illnesses stemming from military deployment can be understood as conditioned responses to chemical odors encountered under stressful conditions (Bouton, Barlow & Mineka 2001). The specific goals of Year 3 were conduct two studies to examine (1) the degree to which a conditioned response could be extinguished by re-exposure to the odor in the absence of the stressor stimulus and (2) to evaluate whether information about the toxicity of the odor could retard the extinction of the conditioned response. We also intended to complete the study exploring the degree to which an ecologically valid stressor (hazard training video) can produce heightened conditioned stress response to odors among professional emergency responders (Study 4); however, difficulties in recruiting and scheduling this study population has delayed the completion of this study. It is anticipated that continued recruitment and study completion will take place during Year 4.

BODY:

Testing of human research participants in the studies listed in the approved SOW for Year 3 continued with Study 4. However, due to multiple scheduling constraints for the planned subject population, this study has not yet been completed, but is still ongoing. While data on the first 15 subjects are presented, we have proposed a modification to this study protocol which we believe will allow us to recruit more efficiently from the target population.

We are in the final stages of testing in Study 5, "Effect of Personality Traits on the Extinction of Odor-Stress Conditioning", having added 12 additional subjects since the first submission of this report and have completed data collection in Study 6. Data analysis is still underway for Study 6, although a number of preliminary results are presented here.

In addition, in Year 3 we have completed writing code in Matlab for the reduction and batch analysis of all physiological data collected in these studies. This will greatly shorten the time necessary for data analysis and improve the quality of the data through systematic scan and removal of artifacts.

General Subject Recruitment and Screening

Participants are recruited using flyers, advertisements placed in local newspapers or selected from our subject database. Individuals who express an interest in participating in our studies are invited for an information and screening session in which they are provided with information about the nature of this study. By signing a special (independent of this study) consent form, they give us permission to collect and store relevant demographic data in our database for the purpose of screening for eligibility for our studies. During the first session, they complete a self-report medical/occupational history and Chemical Intolerance Index (Lees, Stefaniak, Emmett, & Dalton, 2003). They are also tested for their olfactory abilities on a 7-item olfactory discrimination task, to ensure their ability to detect and process the experimental odors (Dalton, Gould, Girten, Stodieck, & Bateman, 2003). For the screening session, they receive financial remuneration of $10. We rely on self-report history with confidence, because it has been our experience that our procedures pose only very minor, if any, risk of physical harm or lasting psychological distress.

Individuals (m/f) between ages 18-55, in good general health, with average olfactory abilities, no occupational history of chemical exposure, no chemical sensitivity, medical diagnosis of cardiovascular disease, or asthma, no pacemaker, and no psychiatric diagnoses of Chronic Fatigue Syndrome, Posttraumatic Stress Syndrome, Depression, Anxiety Disorders, Burnout Syndrome or Claustrophobia are eligible for our experiments. We regularly test an ethnically diverse group composed of roughly equal numbers of males and females (see enrollment tables for each study). However, in order to comply with the experimental instructions, all participants have to be able to speak and understand English well.

Exclusion criteria:

Demographics: criteria related to demographics are collected using the medical/occupational history screening form. Individuals younger than 18 years old and older than 55 years and who are non-English speakers are excluded from our studies.

Chemical Intolerance: Participants who report regular to frequent sickness from chemical, synthetic odors (a score of 3 or above across the board, or some 4's and 5's for chemical odors) are excluded. To date, we have only had to reject two subjects based on these criteria.

Sense of smell: Participants who indicate a sense of smell much worse than most people's, or do not pass the criterion on the 7-term odor identification task are excluded from the study.

Medical criteria: Participants who answered "yes" to any of the following medical conditions will be excluded from the studies: asthma, severe seasonal or perennial allergies, chronic sinusitis, deviated septum, a head injury with loss of conscience, cardiovascular (heart) disease, high blood pressure, or if they have a pacemaker.

Exposure history criteria: Individuals who indicated a prolonged (> 1 year) occupational exposure history to pesticides, industrial solvents or formaldehyde are excluded.

Psychiatric criteria: Individuals who indicated to have or have had any of the following conditions are excluded from participation: Chronic Fatigue Syndrome, Posttraumatic Stress Syndrome, Depression, Anxiety Disorders, Burnout Syndrome or Claustrophobia.

SOW FOR YEAR 2 (delayed, in progress)

Study 4, entitled "Association of An Odor (CS) To Multiple Real-World Stress Stimuli" will investigate the feasibility of a stress induction procedure other than the Trier Social Stress Test for use in the laboratory. Police Academy trainee personnel will watch Police Academy training videos, which are expected to engage their belief-system and, consequently, cause stress and arousal as a US. This stressor is presumed to have more ecological validity than the Trier Test. Study 4 will follow the design of Study 1 as described below; 48 subjects will be tested in two sessions. Measures of autonomic arousal, cognitive function and self-reported stress and health symptoms will be collected.

STUDY 4: Association of an Odor (CS) To Multiple Real-World Stress Stimuli

Study 4

Study 4 is essentially a replication of a prior study (Study 1), with the exception of employing a different stressor for odor- stress-conditioning. Instead of employing as the stressor, the standard laboratory stress manipulation (Trier Stress Test), a complex array of stimuli presumed to have more ecological validity, while still engaging the belief system of the individuals being tested, are used as the US. Thus far, subjects have been selected from law-enforcement personnel or trainees in order to ensure that the chosen stressors adequately engage the belief systems of the

individuals and that the stressors to which they will be exposed will not be significantly greater than those that are experienced in their occupational settings.

Group 1 received a pairing between the novel odor (assumed to be the CS) and the training film (assumed to be the stressor US) or a relaxation film (assumed to be the relaxing US) during the Conditioning Session for a duration of 20 minutes. Group 2 received the same treatment, except with reverse-paired odors. Group 3 received two sessions: the conditioning session involved presentations of the combined USs only followed by presentation of the CS odors alone during the test session to examine the degree to which conditioning can occur to the context (room) alone.

Procedure: A video used for training law-enforcement and emergency responder personnel (e.g., chemical and biological warfare response) consisting of multiple segments depicting re-enactments of such emergencies (stressor US) and videos of meditation procedures (relaxing US) were presented on a large-screen TV placed inside the chamber. The odors were slowly infused into the room while subjects were exposed to the US to allow for association with the stressors. Since the subjects were not occupied with the Trier test, and to ensure attention was being paid to the stimuli, subjects were told they have to answer questions about the video following the session.

Table 1: Enrollment to date in Study 4

	Caucasian	African/ American	Hispanic	Asian American	Other or Unknown	TOTAL
Female	**2**	**1**	**0**	**0**	**0**	**5**
Male	**7**	**4**	**1**	**0**	**0**	**10**
TOTAL	**9**	**5**	**1**	**0**	**0**	**15**

Measures of Stress Response: In this study, as well as all others conducted in this project, we have sought to obtain multiple converging measures of a clinically significant stress response, including self-reported anxiety, cortisol levels (a widely-used measure of stress response), psychophysiological parameters of arousal (including heart rate and electrodermal activity), perceived health symptoms and performance disruption on a standardized memory test (the California Verbal Learning Test). While none of these measures by themselves may be indicative of clinically significant levels of stress, we are aiming to develop a profile that may be predictive of a stress response in a real-world situation. Thus, some of the measures are largely

exploratory ones, while others (self-reported stress and cortisol response, memory disruption) have considerable validity in the realm of stress research.

Initial responses suggest a wide variability in autonomic responses to the stressors within this cohort. However, the small sample size (n=5/gp) precluded any formal analysis to determine significance. We do intend to correlate changes in autonomic response to the stressor with personality subtypes (e.g., Negative Affectivity) in order to partition out some of the variation in response, if it is due to differences in personality traits.

Progress to date: Although we piloted the training videos in Year 2 and selected several potential pools of individuals to participate in this study, we have experienced difficulties in scheduling the target population to attend the studies. Our recruitment has been much slower than anticipated, and thus we have tested only 5 individuals in each group. Fortunately, as a consequence of working with firefighter populations for an NIH-funded clinical study, we have recently initiated closer contacts with local firefighters who have expressed interest in participation. Thus, we anticipate being able to continue to recruit and schedule participants in this study throughout Year 4, however only if we can shorten the procedure along the lines proposed below.

Suggested Modification to Study Design: A change in the protocol has been contemplated which we believe will greatly facilitate subject recruitment. In all prior studies, incorporating both the stressor and relaxation phase in each session caused the session to exceed 2.5 hours per day (and in some cases, it exceeded 3 hours/ session). We were able to recruit very few subjects, meeting our eligibility criteria for this study, who were able to participate for the necessary time commitment. Hence, given the importance of demonstrating a conditioned stress-response to an odor cue under more environmentally realistic conditions, we propose to omit the second part of the session during which odors are paired with a relaxation induction in order to keep the session under 1.5 hours per day and allow us to collect data in a reasonable pace. This is viewed as especially important given the impact on the project timetable that occurred following the delay in obtaining HUC approval during all of Year 1. However, in order to ensure that the subject will not be stressed when leaving the session, we will have them participate in the relaxation induction in a separate room, but without collecting physiological data and in the absence of any odor. Consequently, this should not require any significant modification to the description of the procedure in the consent form. We piloted this procedure

with 4 subjects and observed that self-reported stress levels following this 5-min relaxation session were lower than during the odor-stress conditioning phase which preceded it, thus ensuring that the subject would leave the experimental session without undue stress.

We do not feel this will compromise the value of the study findings, as the main focus of the study is to determine if an odor-stress association can occur using somewhat more environmentally realistic stressors. Given that conditioning of an odor to a relaxation state in one pairing results in relatively little evidence of conditioning response on any of the physiological measures, we do not feel this provides much of value to the continuing studies. Subjects did report liking the odor paired with relaxation more in the prior studies, but this effect does not represent a novel finding, and in the interest of studying phenomena relevant to Gulf War Syndrome, we would like to optimize our efforts and conduct this study using only the stress-odor conditioning condition. The table below represents the new proposed design (strikeouts indicate changes from the prior design.).

Design: Table 2. Proposed New Design of Study 4

Group	Conditioning Phase	Test Phase
1 (Congruent)	CS_b + 20 min.stressor ~~CS_a + 20 min. relaxation~~	CS_a - HR/Resp/Startle/Cog. ~~CS_b - HR/Resp/Startle/Cog.~~
~~2 (Incongruent)~~	~~CS_a + 20 min.stressor~~ ~~CS_b + 20 min. relaxation~~	~~CS_a - HR/Resp/Startle/Cog.~~ ~~CS_b - HR/Resp/Startle/Cog.~~
3 (Control)	+ 20min. stressor ~~- 20 min. relaxation~~	CS_a - HR/Resp/Startle/Cog. ~~CS_b - HR/Resp/Startle/Cog~~

Design: Group 1 will be exposed to the odor in the presence of the stressor for a period of 20 minutes. Due to the proposed elimination of the relaxation condition, there is currently no need to test a second group with an alternate odor. This elimination will allow us to add additional subjects to each of the remaining conditions (Group 1 and Group 3). A control condition, Group 3, will be exposed to the US (stressor) but without an odor, in order to evaluate the strength of conditioning that occurs to the context (room) alone. During the conditioning phase and the test phase, we will monitor heart rate and respiration rate of each participant, as measures of autonomic arousal; we will also evaluate subjective symptom reports and mood. The test phase will utilize these measures as well as several additional dependent measures, including a test of cognitive function (short-term and general memory performance). In both conditioning

and test phases we will collect salivary samples 8 times in order to measure cortisol levels. Twenty-four subjects will be tested in each group, yielding a total of 48 subjects.

Procedure: The study is introduced to the subject as a study about the influence of odors on cognitive performance and attention. The timetable and schedule of dependent measures will remain as indicated in Table 2. During Session 1 (the conditioning session), the subject will fill out personality questionnaires for half an hour, to allow for serum cortisol levels and any anticipatory stress related to participating in a study to decrease to a comfortable baseline level. Thereupon, the subject enters the environmental chamber, where electrodes are connected to the subject's body for 10 minutes of baseline biomonitoring of autonomic endpoints. After 10 minutes have elapsed, the subject is shown a training video which portrays the outcome of a biological/chemical warfare attack and the actions to be taken by emergency personnel under such circumstances. During this session, subjects in one group are exposed to the odor while subjects in the other group do not experience an odor. Once the odor is dispersed into the room, they complete sensory ratings while various physiological endpoints are measured (see Table 3).

Measures:

Table 3: Study 1, Sessions 1 and 2: Timetable of events and endpoints

Prechamber		Chamber	Session 1: Odor a/b + Stressor Session 2: Odor a/b + Test					
	T-40	T-10	T0	T+10	T+20	T+30	T+40	T+50
Questionnaires	X							
Cortisol	Y	Y	Y	Y	Y	Y	Y	Y
VAS	Y	Y	Y	Y	Y	Y	Y	Y
Symptom		Y			Y			Y
Mood		Y			Y			Y
Intensity ratings		Y*						
HR/Resp/EDA		Y**						
Memory			Z**			Z**		

Note: The symbols X, Y, Z denote when the given measures were collected: X was measured only during Session 1, Y during both Session 1 and 2, and Z only during Session 2.
* Odor intensity ratings were collected every 5 minutes throughout the stay in the chamber
** These measures were collected continuously throughout exposure
VAS = Visual Analog Scales, HR= Heart Rate, Resp = Respiratory Rate, EDA=Electrodermal Activity,

The following endpoints were measured *at both conditioning and test sessions*:

Stress: Salivary samples for cortisol assessments were obtained upon arrival (Baseline 1: T-40), just prior to entering the chamber (Baseline 2:T-10), 10 minutes after entering chamber (Baseline 3:T0), 10 minutes into the preparation for the TSST (T+10), 10 minutes into the performance phase of the TSST (T+20), and 10, 20, and 30 minutes into the relaxation phase (T+30, T+40, and T+50). Subjective ratings of perceived stress and anxiety were rated on Visual Analogue Scales at the same time-points when saliva samples were obtained. Saliva samples were obtained by having subjects chew on a salivette for 2 minutes, which were then expectorated into a vial. Vials were centrifuged and the resulting supernatant was transferred into a cryo-vial and kept frozen at -80 C, until transferred to the laboratory for analysis.

Odor, irritation and annoyance intensity ratings: While in the chamber, the subject rated the intensity of the odor, sensory irritation and annoyance on a computer version of the Labeled Magnitude Scale (LMS) every five minutes. The LMS is a category-ratio scale that has ratio properties while using category labels to guide the placement of the rating (Green et al., 1996). Ratings can range from no sensation to strongest imaginable.

Mood State: Current mood states were assessed, using the Profile of Mood States, just prior to entering the chamber and after the CS+ and CS-conditions (McNair, Lorr, & Droppleman, 1992).

Health symptoms: Health symptoms were rated on a laptop just prior to entering the chamber, and after the CS+ and CS-conditions. Health symptoms were grouped into seven categories: cognitive, sensory irritation, central nervous system, autonomic, respiratory, GI and sham (Smeets, Maute, & Dalton, 2002).

Autonomic arousal: Respiratory rate/volume, heart rate and electrodermal activity were continuously monitored throughout baseline, the stressor task and the relaxation phase, using the Lablinc V system (Coulbourn, Allentown, PA).

The following endpoints were measured *only during the test phase*:

Cognitive Function: To evaluate the degree to which conditioned stress can impair cognitive function, we administered the California Verbal Learning Test (CVLT) as a measure of learning and memory compared with the subject's own assessment of their performance on these tests. The CVLT was administered only during the test session. Because subjects' evaluations of their performance on neuropsychological tasks have been found to be more closely related to affective distress than to actual performance (Binder et al., 1999), subjects also rated their performance on a 10 point Likert Scale.

TAKEN FROM THE SOW FOR YEAR 3

Study 5, entitled "Effect of Personality Traits on the Extinction of Odor-Stress Conditioning" will explore whether exposure to the conditioned stimulus odor in the absence of the stressor will extinguish the conditioned responses. This study will also determine whether individuals who rank high on a personality trait known as "negative affectivity" (NA) will exhibit slower extinction of any conditioned autonomic, stress or health symptoms than individuals who rank low on this trait. 64 volunteers (half high NA, half low NA) will be tested in three sessions during which they will be exposed to a neutral and an unpleasant odor paired or

unpaired with a stressful or relaxing task. Measures of autonomic arousal, cognitive function and self-reported stress and health symptoms will be collected.

Study 5: Personality Traits & Extinction of Odor-Stress Conditioning

Aim: If the unconditioned stimulus (US) never again follows the conditioned stimulus (CS), conditioning will *extinguish*. In other words, if stress never again is induced in association with the CS, the CS will lose its ability to elicit the autonomic stress response and related health symptoms (Van den Bergh et al., 1999). However, subjects who are very susceptible to stress may have become more fearful, anxious or anticipating of the odor and its effects than subjects who are not susceptible. During the Gulf War, soldiers will have varied in the extent to which they were affected by war conditions as a function of personality traits. In Experiment 5, two groups of subjects were selected-- subjects with high scores on neuroticism and negative affectivity and subjects with low scores on these characteristics (Watson & Pennebaker, 1989). Because we pre-test and select participants at each end of the potential range of NA, we are more likely to see significant associations of NA and chemosensory response in small samples. Both groups received stress-odor conditioning to the CS in Session 1. An extinction session followed in which subjects were exposed to the CS (odor) but not the US (stressor), to evaluate the reduction in autonomic response and health symptoms over time in general, and also as a function of personality traits, as described below.

Table 4. Design of Study 5

Group	Conditioning Session	Extinction Session	Test Session
0 - Hi NA + Neu	CS_b + 20 min.stressor	20 min. room exposure	CS_a - HR/EDA/Cog.
0 - Lo NA + Neu	CS_a + 20 min.stressor	20 min. room exposure	CS_a - HR/EDA/Cog.
1 Hi NA & Neu	+ 20min. stressor	20 min CS_a	CS_a - HR/EDA/Cog.
1 Lo NA & Neu	+ 20min. stressor	20 min CS_a	CS_a - HR/EDA/Cog.

Subjects: Fourteen subjects have been tested in each group, yielding a total of 56 subjects (out of a proposed total of 64). The ethnic and gender breakdown are presented in Table 5. Average age of the subjects were 32.4 for the females, 29.5 for the males. Data collection in this study was incomplete at the time of the original submission of the annual report, however we have continued to recruit in order to increase the power to the proposed level in the original proposal.

As other investigators have noted, a major issue with studies of NA is that individuals with high scores on this dimension tend to be unreliable subjects and do not always complete the sessions. This can greatly retard data collection efforts.

PROCEDURE: Subjects participated in three sessions, tested individually. The procedure for eliciting stress during the conditioning session was identical to that described in the previous studies, with subjects exposed to a neutral odor paired with a modified version of the Trier Social Stress Task (TSST). The TSST is a mental stress provocation task consisting of a 10 minute preparation/anticipation phase and a 10 minute performance-under-stress phase (Kirschbaum, Pirke, & Hellhammer, 1993). The subject was given 10 minutes to prepare a 5 minute oral speech which was recorded on videotape to be evaluated by a panel of judges. (Unlike in the real TSST, no evaluation actually took place). The instruction coincided with the dispersion of a detectable concentration of the Conditioning Odor, which is either CS_a or CS_b. After 10 minutes of preparation, the experimenter announced the end of preparation and the start of the speech via intercom, and the videotape was started. No videos of the subject's performance were actually kept or judged and each was overwritten at the start of the next session (or erased, whichever was more feasible). Following the public speaking phase, the subject was switched to the mental arithmetic portion of the task, which required the subject to perform serial subtraction aloud. Whenever necessary, the experimenter prompted the subject via intercom to increase their speed, to begin over (when a mistake was made), etc.

Two days later, subjects returned to the laboratory for the extinction session and two days after that, for the test session. During Session 2, Group 1 was given a 20-minute exposure to the conditioning odor in the same room as which conditioning occurred, during which no measures were taken. Subjects in Group 0 were given exposure to the room, with no conditioning odor present; thus, for this group we anticipated that extinction to the odor would not occur (although extinction to the room context may be taking place). Two days following that session, they were again exposed to the conditioning odor in the same room while the various endpoints were being measured, including self-reported stress, salivary cortisol, electrodermal response, heart rate, respiration, health symptoms and memory measures.

Table 5. Enrollment of participants in Study 5 (updated 1/5/05)

	Caucasian	African/ American	Hispanic	Asian American	Other or Unknown	TOTAL
Female	**13**	**12**	**2**	**1**	**0**	**28**
Male	**10**	**12**	**4**	**0**	**2**	**28**
TOTAL	**23**	**24**	**6**	**1**	**2**	**56**

Hypothesis: It was expected that the autonomic stress responses and health symptom reports exhibited by subjects in Group 1 would be lower (i.e., show effects of extinction) than those exhibited by subjects in Group 0, who did not have an odor extinction session. We also hypothesized that personality features would be important mediators in the magnitude and persistence of the conditioned stress response and that Group 1 (High NA and neuroticism) would exhibit slower extinction of the autonomic stress and self-rated stress response as compared with Group 2 (Low NA and neuroticism).

Data Analysis:

Using an omnibus MANOVA, we first evaluated the impact of odor (unpleasant or neutral) on the responses to the stress and relaxation sessions on Session 1 vs. Session 3. There was no main effect of odor on any of the responses, $F_{(1,52)} = 2.27$, $p > .1$ (including rated intensity and annoyance), suggesting that both hedonically congruent and incongruent odors were equally effective (or ineffective) at influencing the unconditioned response on Session 1 and the conditioned response on Session 3.

Next, we evaluated the main effect of conditioning (stress vs. relaxation) and found a significant overall effect of conditioning type, $F_{(1,52)} = 21.6$, $p < .05$. However, while responses on both sessions to the relaxation condition differed from those in the stress condition, there was no evidence of conditioning to relaxation (as measured by responses to the odor paired with relaxation on Session 3) on any measure except odor liking, and this is likely to represent a mere exposure effect. Thus, for simplicity and to focus on the clinical condition of interest, stress, the results reported here focus only on the responses obtained in the stress sessions, comparing the group that experienced extinction to the odor with the group that did not.

Data were analyzed using a mixed-model Analysis of Variance (ANOVA), with a 2 (Condition: extinction vs. none) X 2 (NA- high vs. low) X 2 (Session- 1st vs. 3rd) design.

Subjective ratings of stress: There was a main effect of extinction condition on perceived stress response, $F_{1,52} = 4.75$, $p < .05$ and a main effect of personality (negative affectivity) as well, $F_{1,52} = 4.18$, $p < .05$. Individuals who were exposed to the odor during the second session

rated stress lower in Session 3 than did individuals who were not re-exposed to the odor. Individuals who were high in NA ($F_{1,52} = 5.01$, $p < .05$). Perhaps most interestingly, there was a significant interaction between extinction condition and personality ($F_{1,52} = 5.15$, $p < .05$. Figure 1 shows the self-rated stress during Session 3 for each of the four groups separately (Group 0 received no extinction, Group 1 received extinction trial during session 2). The loss of the conditioned response to the odor was greater for individuals who were low in NA than it was for those scoring highly on the NA dimension. Similarly, the loss of the CR to the context was greater for the low NA group than for the high NA group. These results suggest that a high NA individual who develops an odor-stress association may require more extinction sessions in order to reduce the conditioned response to the odor.

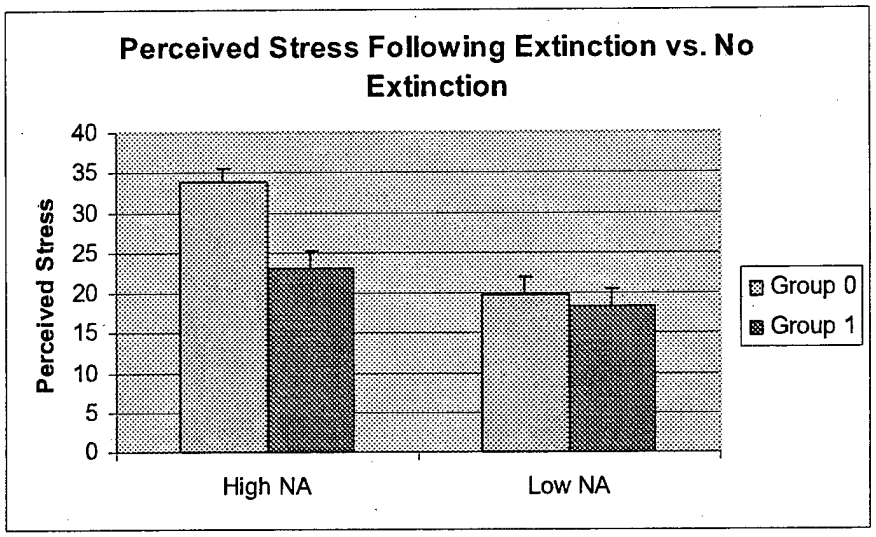

FIGURE 1: Self-reported stress on Session 3 (overall) as a function of group and personality. Stress ratings were made using a visual analogue scale ranging from 0-100 cm, where 0= no stress and 100= extreme stress.

Salivary Cortisol: Saliva samples were obtained at multiple timepoints during the first and third session in order to observe whether there were any stress-related increases in cortisol upon initial exposure and re-exposure to the odor during the test session. The samples from only the first 48 subjects have been analyzed. In contrast with the self-reported stress ratings, there were no significant differences between cortisol responses as a function of extinction condition, however there was a main effect of NA on cortisol response, with individuals scoring high on the NA dimension having higher baseline cortisol and higher stress-associated cortisol on both sessions,

($F_{1,44} = 5.12$, $p < .05$). Figure 2 depicts the cortisol levels for both NA groups on Session 3. The interaction between extinction condition and NA did not reach significance, ($F_{1,44} = 3.56$, $p = .09$). As noted in previous studies, both baseline cortisol levels and changes appear to be quite heterogenous, with some individuals showing large increases upon response to the stressor (and the subsequent re-exposure to the odor) while some individual who nonethleless, report feeling stressed do not show much of an elevation in salivary cortisol. The elevation in cortisol response for some individuals could be considered clinically significant elevations in stress response, but overall the variance we observe suggests that salivary cortisol may not be the most reliable marker of stress across all individuals. Given the number of samples we obtain (n=8) in each session it is unlikely that we are missing any transient elevations that may be linked to the stress response, although there is still a possibility that the response is significantly delayed in some individuals and that elevations do not occur until after the experimental session has ended.

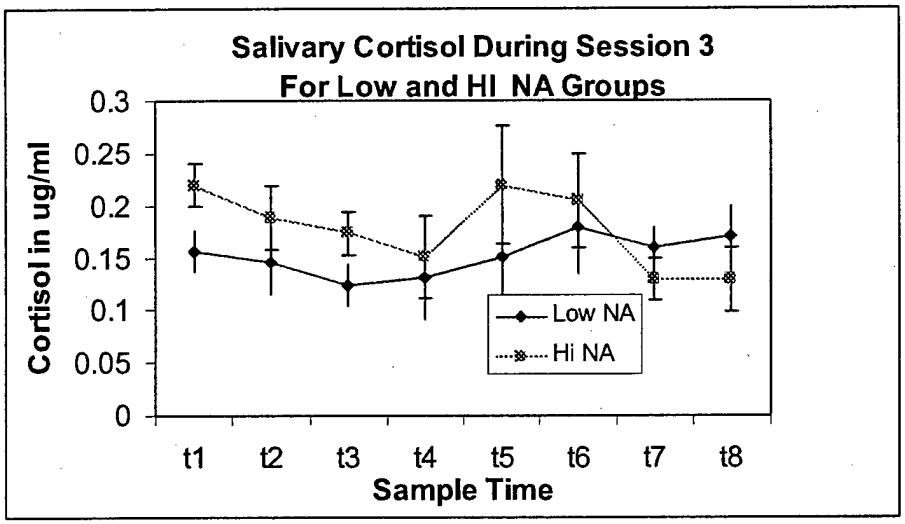

Figure 2. Cortisol response across the multiple timepoints in Session 3. Salivary samples for cortisol assessments were obtained at 10 minute intervals throughout the session: upon arrival (Baseline 1: T-40), just prior to entering the chamber (Baseline 2:T-10), 10 minutes after entering chamber (Baseline 3:T0), and at 10 minute intervals thereafter. T8 is taken 10 minutes after exposure ends.

Performance on CVLT: Disruptions in cognitive performance, especially memory tasks, is one of the primary complaints of Gulf War veterans. Accordingly, we evaluated the degree to which conditioned stress could disrupt cognitive processing using the California Verbal Learning Test.

We evaluated multiple dimensions of performance on the CVLT, including number correct on free recall, number of repetitions and number of intrusions (items reported as being on the test which were not actually presented).

CVLT Results on Session 3

Group	Correct Recall	Repetitions	Intrusions
Low NA	6.45	1.8	1.67
High NA	6.55	2.1	3.7

ANOVA analysis revealed that overall CVLT recall performance did not differ between the extinction conditions for the two groups, $F_{(1,52)} = 1.29$, $p>.1$ ($M = 6.45, 6.55$). However, there was a significant interaction between NA and performance type (Recall, Repetitions, Intrusions) in which the high NA group exhibited significantly more intrusions when re-exposed to the stress associated odor than did the low NA group, $F_{(1,52)} = 4.51$, $p <.05$; (mean difference in # of intrusions between NA conditions = 3.7, & 1 .67, respectively). In addition, the high NA group reported poorer memory performance on the test phase than did the low NA group (7.84 vs. 4.01 on a 10 point visual analog scale, respectively). This finding continues to be of interest given the reported claims among GW veterans of poorer memory performance, which are not always observed when tested using standard memory measures. In brief, this suggests that stress may interact with perceived effort such that cognitive processes are judged as more effortful and less efficient, even if the outcome on performance is the same. The increased perceived effort might have detrimental implications for information-processing under deployment situations.

Electrodermal response (EDR): To measure the degree of arousal orientation to the odor cue, skin conductance (EDR) was measured throughout each phase, although the analysis was confined to 1-minute epochs surrounding each of the timepoints where experimental manipulations occurred. Of greatest interest in this study was to observe whether the phasic EDR, which was time-locked to certain experimental manipulations, differed during session 3 as a function of extinction condition. Figure 3 presents the EDR response across the multiple time points of Session 3 expressed in microsiemens. Upon re-exposure to the odor in session 3, there was an increase in EDR for the group that did not receive extinction (white symbols) when compared with the group that was re-exposed to the odor without the stressor (black symbols),

but this increase was not significant at the level of p = .008 (Bonferroni correction for multiple comparisons).

The magnitude of any phasic response to a stimulus can range from 0.5 to 5 microsiemens. Thus, while the average amplitude of the phasic response, less than 1.5 microsiemens, is not very impressive, there does appear to be a mild orienting response to the introduction of the odor in the group that had no extinction vs. the group that did. However, the amplitude of the EDR was higher at the start of the memory task, suggesting that the combination of odor + additional stress may have a greater impact than just exposure to the odor or the additional stress alone (note: no change in EDR for the group receiving extinction at the start of the CVLT). In general, EDR response should be considered merely an exploratory measure which can signify autonomic arousal, and tying the actual levels of the phasic response to a clinically significant stress level is problematic. Hence, at the present time, we look more toward the self-report and behavioral responses to indicate the presence of conditioned and extinguished stress response.

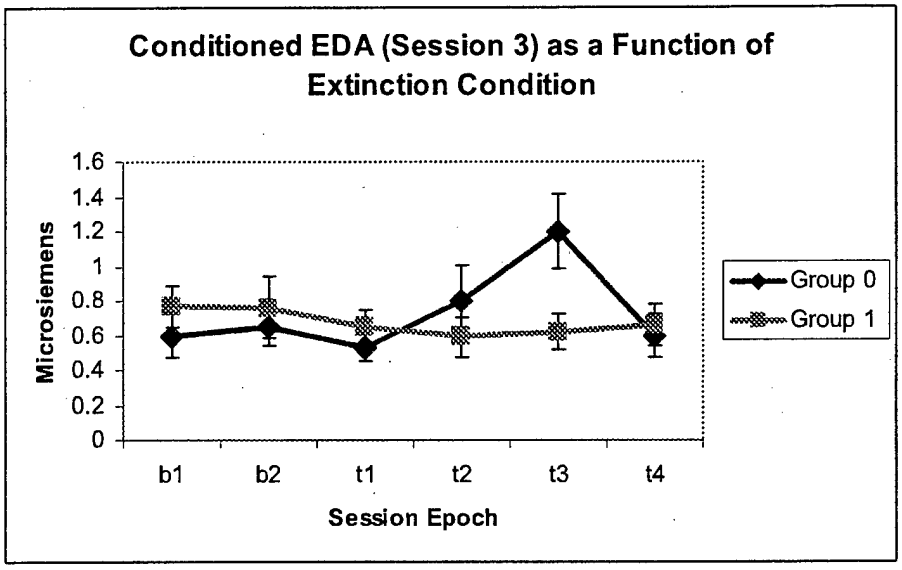

Figure 3: Electrodermal response as a function of the extinction manipulation. Filled symbols represent the averaged response of the group that did receive extinction session, Open symbols represent the no-extinction group. Typical range of EDA is 0.5-5.0 microsiemens. B1= initial baseline in chamber, B2=10 min after entry into chamber, T1=introduction of odor into chamber & buildup (respirator on), T2=removal of respirator/odor cue, T3= start of CVLT , T4=end of exposure.

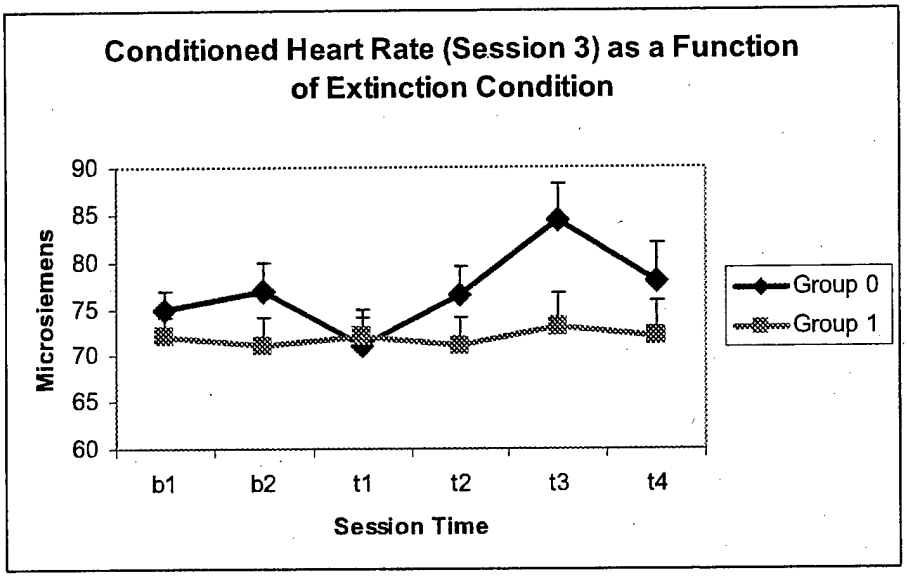

Figure 4. Heart rate during session 3 as a function of extinction condition. Time points on the X axis signify the same events as shown in Figure 2.

Heart Rate: ANOVA performed on the heart rate in session 1 and 3 revealed a marginally significant effect of extinction condition, $F_{1,52} = 5.25$, $p < .01$ ($p = .008$ after Bonferroni corrections). The average heart rates during session 3 mirrored the self-reported stress results and thus differed as a function of whether the group received the extinction session (i.e., were re-exposed to the odor) or did not (i.e., were only re-exposed to the context). Average HR (in beats per minute) for the group re-exposed to the odor during phase 2 was stable across the session and lower during re-exposure to the odor than for the group that did not receive the extinction session (M=75.5 vs. 80.1, respectively).

Reported Health Symptoms: Participants rated a variety of health symptoms immediately before and at the end of exposure on Days 1 and 3. 25 health symptoms were rated and for analysis, classified into 7 subgroups: Autonomic nervous system, gastrointestinal, central nervous system, cognitive, respiratory, irritation. To control for bias to respond, a number of control symptoms were also rated (i.e., leg cramps, tooth pain = sham condition).

There was no main effect of extinction condition on health symptoms, $F_{(1,52)} = 3.21$, $p > .1$. However, there was a main effect of personality (NA) on symptom reports, $F_{(1,52)} = 7.75$, $p < .05$)., with individuals who scored high on NA reporting significantly more health symptoms at baseline and test than individuals who scored low on NA. This is not surprising, given that NA

is closely related to health symptom perception. However, there was a significant interaction between extinction condition and health symptom groups, $F_{(6, 312)} = 3.56$, $p < .001$ (Bonferroni corrected p value of .007 for significance). Post hoc tests revealed that only the respiratory symptoms and cognitive symptoms differed between groups, both at $p < .001$. No other subgroups of symptoms differed between the group receiving the extinction session and the group that did not.

Implications of Study 5 results: Despite the fact that the overall magnitude of the conditioned response on any measure was not extremely robust in this study, we still found evidence that a single re-exposure to the odor without the stressor present was capable of somewhat reducing the conditioned response on a subsequent re-exposure. This suggests that under controlled circumstances, re-exposure to the conditioned stimulus that elicits stress may be effective in reducing the conditioned stress response. Also of interest was the observation that physiological responses to an additional stressor (memory test, CVLT) were enhanced for the group that did not receive extinction to the odor, suggesting that once an odor has come to signal a stress response, experiencing it again under stressful conditions may magnify the response. However, it should be acknowledged that the overall magnitude of the conditioned stress response was significantly lower than what might be expected under real-world deployment situations and hence, the extrapolation of this manipulation to actual situations should be cautiously evaluated. In the final studies of this project, we hope to increase the magnitude of the conditioned response in order to determine whether extinction and/or blocking of such response are a viable option for deployment stress. The major concern with such a experimental manipulation is to ensure the safety and comfort of the participants.

The observation that personality traits such as NA are related to the magnitude and persistence of the conditioned stress response to odors and environments suggests it may be a useful tool to predict individuals' reactions to combat situations. In other words, certain personality dimensions may function as mental health baselines for psychological status and suitability for given assignments. It has been suggested that, in addition to its status as a personality trait, NA can serve as a proxy for chronic stress or 'burnout'. To determine if this is the case, and to observe whether levels of chronic stress interact with phasic stress events, future studies conducted under this effort will incorporate a measure of chronic or generalized stress, as

indexed by Cohen's Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983) or a similar instrument.

Study 6: Extinction vs. Cognitive Sensitization

TAKEN FROM THE SOW FOR YEAR 3

Study 6, entitled "Extinction vs. Cognitive Sensitization", will investigate whether information about the potentially hazardous nature of a previously exposed odor can lead to sensitization of the odor-stress response and thereby retard extinction. 48-64 volunteers will be tested in three sessions in which they will be exposed to two hedonically neutral odors that have been given either a neutral or a negative characterization, as relates to long-term health effects. Measures of autonomic arousal, cognitive function and self-reported stress and health symptoms will be collected.

Aim: In prior studies of animal conditioning, if a CS (odor) is not re-paired with the US (stressful situation), the conditioned response to the CS odor does not always completely extinguish. Several possibilities have been suggested to account for a failure to extinguish the conditioned response. For example, extinction may be prevented from occurring if the respondent avoids remaining in the presence of the CS for a sufficiently long period of time in order to learn the lack of contingency between CS-US. Alternatively, the occurrence of the CS may elicit such a vivid memory of the original US, along with anxiety and stress responses, that the original contingency is again re-learned. And finally, additional information that may be acquired about the significance or meaning of the CS can serve as a new US, and perpetuate the original stress/autonomic response to the CS. In the latter case, exposure to media concerns about the possibility of chemical exposures in the Gulf War may have acted to sensitize individuals to the meaning and significance of the odors experienced in initially stressful circumstances.

DESIGN: To explore this possibility, we first conditioned and then attempted to extinguish the association between a neutral odor and a stressful task, using the design of Experiment 5. In this design, subjects experienced the laboratory Trier Stress Test in the presence of an unfamiliar odor (hinoki/galbanum) on the first session. On the second session, they were re-exposed to the odor without any stress manipulation. However, immediately prior to the extinction session, individuals were given one of three types of information about the odor to which they were initially exposed and would be again: Group 1 was told the odor was a natural extract (positive), Group 2 was told the odor was an agricultural pesticide additive (negative). Group 3 was not given any characterizing information (neutral). 16 subjects have been tested in each of the first

two groups, 17 in the third group yielding a total of 49 subjects (data from one subject in group 3 was dropped for apparent failure to understand and follow experimental instructions). The mean age for female participants is 29.8, the mean age for males is 28.4.

Table 6. Enrollment to date in Study 6 (updated as of 12/22/04)

	Caucasian	African/ American	Hispanic	Asian American	Other or Unknown	TOTAL
Female	**11**	**11**	**0**	**1**	**0**	**23**
Male	**8**	**18**	**0**	**0**	**0**	**26**
TOTAL	**19**	**29**	**0**	**1**	**0**	**49**

Hypothesis: We hypothesized that new, negative information about the nature and effects of the odor that an individual was exposed to on the first session may sensitize an individual and thereby retard extinction of the conditioning effects from the US-CS pairing. Specifically, we predicted that the autonomic, stress and health symptom response of subjects in Group 2, who have received the negative characterizing information about the odor, would be higher on Session 3 as compared to Groups 1 and 2. Their performance on the CVLT would also differ, as would their self-rated effort and performance.

Data Analysis: Following completion of testing in early December 2004, data analysis is still in progress. However, a number of preliminary results are reported here.

Data were analyzed using a mixed-model Analysis of Variance (ANOVA), with a 3 (Condition: positive, negative, neutral) X 2 (Session- 1^{st} vs. 3^{rd}) design.

Subjective ratings of stress: There was a main effect of condition on perceived stress response, $F_{2,45} = 4.17$, $p < .05$ and a marginally significant effect of session (1^{st} vs 3^{rd}, $F_{1,45} = 2.9$, $p > .09$). This was largely due to a significant interaction between odor characterization and session ($F_{2,45} = 5.76$, $p < .05$). Individuals who were exposed to the odor during the second session with a negative characterization rated stress higher than did individuals who were given a positive or neutral characterization. Figure 5 shows the self-rated stress using the visual analog scale (ranging from 0-100) during Session 3 for each of the three groups separately. The group receiving negative information about the chemical stimulus rated stress significantly higher when compared to the groups receiving positive and neutral information (M = 48, 21 and 28, respectively) on session 3, but not on session 1.

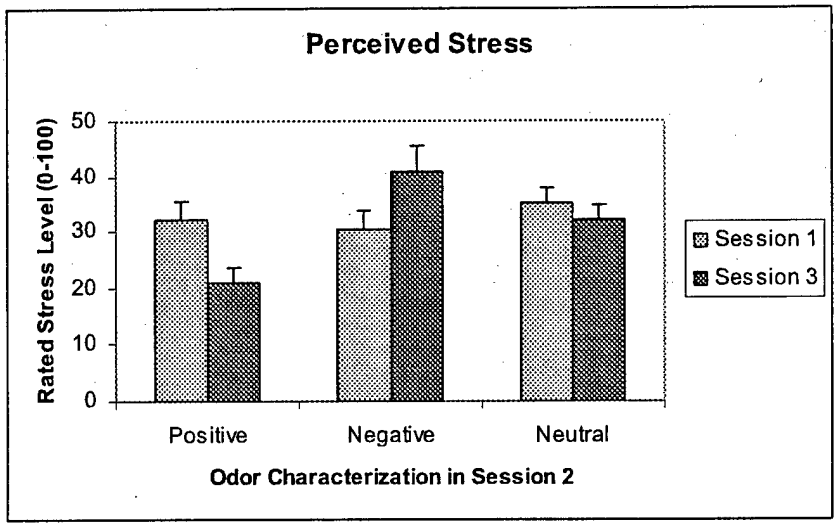

Figure 5. Rated levels of self-perceived stress in the conditioning session (1) and the test session (3) as a function of how the odorant was characterized during session 2. Ratings were made using a visual analog scale that ranged from 0 (no stress) to 100 (extreme stress).

Salivary Cortisol Analysis of salivary cortisol in this study is unfortunately, still in progress due to scheduling constraints of the Diabetic Research Laboratory at the University of Pennsylvanaia. We anticipate laboratory results in late January, 2005.

Performance on CVLT: As in prior studies, we evaluated multiple dimensions of performance on the CVLT, including number correct on free recall, number of repetitions and number of intrusions (items reported as being on the test which were not actually presented).

Group	Correct Recall	Repetitions	Intrusions
Positive	6.75	.75	1.1
Negative	5.75	4.1	3.2
Neutral	6.25	1.1	1.9

Analysis of variance performed on the free recall, repetitions and intrusions revealed a main effect of group (odorant characterization), $F_{(2, 45)} = 5.12$, $p < .05$. We also observed a significant interaction between odorant characterization and performance type (recall, repetition, intrusion), $F_{(4, 90)} = 2.95$, $p < .05$. The group given a positive characterization had fewer repetitions than those given the negative characterization, while the group given the negative characterization also produced the highest number of intrusions (items which were recalled, but

which were not actually presented). Free recall performance during re-exposure to the odorant in session 3 did not differ as a function of how the odorant was characterized prior to the extinction session. Group Negative also reported poorer memory performance on the test phase than did the other two groups (3.42 vs. 8.01 and 6.51 on a 10 point visual analog scale, for the negative, positive and neutral group respectively), but only the comparison between the positive and negative group reached significance.

Electrodermal response: Skin conductance was again measured throughout each phase, although the analysis was always confined to averages during 1-minute epochs surrounding each of the timepoints where experimental manipulations occurred. The main comparison we have completed thus far is to observe whether the phasic skin conductance response to the reintroduction of the odorant during session 3 differed as a function of how the odorant was characterized on session 2. There is a non-significant effect of Group, $F_{(2,45)} = 4.52$, $p = .04$ (Bonferroni corrected p value of .008), with only observable differences between the positive and negative characterizations at reintroduction to the odor, but not between the neutral and any other condition.

Heart Rate: The average heart rates during session 3 also differed as a function of whether the group received positive or negative characterization of the odorant, but the main effect of condition was only marginally significant $F_{(2,45)} = 5.93$, $p = .02$, when corrected for multiple comparisons ($p = .008$). Upon closer inspection it was obvious that this marginally significant effect was due to differences between the positive and negative group only, 75.5 bpm vs. 80.4 bpm, respectively (positive and neutral (78.2 bpm) did not differ, nor did neutral and negative).

Reported Health Symptoms: Participants rated a list of health symptoms immediately before and at the end of exposure on Days 1 and 3, using a 0-5 point scale in which 0 was used to signify they were not experiencing that symptom while 5 indicated they were experiencing the symptom to a great degree. As before, 25 health symptoms were rated and for analysis, they were classified into 7 subgroups: autonomic nervous system (ANS) gastrointestinal (GI), central nervous system (CNS), cognitive (COG), respiratory, irritation (RI). To control for bias to respond, a number of control symptoms were also rated (i.e., leg cramps, tooth pain = sham condition).

There was both a significant main effect of odorant characterization condition on health symptoms, $F_{(2,45)} = 4.25$, $p < .05$ and an interaction between health symptom type and characterization condition, $F_{(4,90)} = 5.48$, $p < .001$ (Bonferroni corrected p value of .007). Individuals given the negative characterization reported significantly more health symptoms in the CNS, respiratory and Cognitive category than did individuals in all other conditions. This is consistent with other studies in which we have manipulated the expectations of health effects from an odorant and suggests that even when the characterization is not explicit on the first exposure, it is possible to add to the perceived hazard level of the exposure with information available on a subsequent re-exposure.

Implications of Study 6 results: Consistent with prior studies that have shown that characterizing an odorant as potentially hazardous can exacerbate responses to that exposure on multiple dimensions (Dalton, 1996; Dalton, Wysocki, Brody, & Lawley, 1997), we found that mischaracterizing the odorant prior to the extinction phase did retard extinction of conditioned stress, for the group that had the odorant characterized as 'negative'. This suggests that belief systems, whether intrinsic or influenced by social or media cues, may be playing a role in the persistence of any adverse response to a conditioned stressor. While the study does not directly address the issue of whether beliefs about chemical exposures during the Gulf War may have increased the magnitude and persistence of any stress response veterans have experienced sine then, it is highly suggestive that such a mechanism may be playing a role.

Overall Implications: It is possible that during the Gulf War soldiers began to avoid the conditioned stimulus (e.g. a specific odor), or had repeated vivid memories of it, or received information about it through the media or otherwise. All of these may have prevented an extinction response to the CS, even if it occurred in the absence of the US. We are seeking to determine whether the physiological effects in this study establish the viability of such a mechanism.

To evaluate whether the results observed in the current studies represent clinically significant levels of stress is a difficult endeavour. To be sure, there are some consistent responses under stress conditioning and re-exposure that would seem to indicate a reliable production of a stress response to an odor cue. However, the correlation between cortisol increase (or any other psychophysiological measure)and self-perceived stress or performance disruptions on memory test are inconsistent across subjects, suggesting that even in the presence/absence of a hormone response an individual may experience stress and this stress may interfere with performance and ultimately lead to health problems. The failure to find strong correlations between objective and

subjective measures of stress and performance measures is not unique to these studies (e.g., (Karkow et al., 2004), but suggests that other variables which are not currently being measured may contribute to one or more measures of the stress response. To this end, in future studies we will obtain measures of chronic stress, as well as evaluate factors that may contribute to the stress response in general, such as sleeplessness, exhaustion, degree of social support, etc. (Dahlgren, Akerstedt, & Kecklund, 2004; Rosal, King, Ma, & Reed, 2004).

HUMAN SUBJECT PROTECTIONS

In response to initial concerns raised by the Institutional Review Board of the University of Pennsylvania and the Human Use Committee of the Army, we have taken additional measures to ensure the protection of subject participants in the studies described herein. In particular, one concern was expressed regarding the potential of the study manipulations introducing into participants an ongoing aversion to certain odors.

We acknowledged upfront that such a potential is present. To preclude this possibility, we continue to employ odors that are uncommon and dissimilar to odors generally experienced in the environment. Odors that we employ are a blend of *hinoki* and *galbanum*, odors, which are familiar in other cultures (Japan) but are very unfamiliar to the western world. Another odor we employ is a fragrance blend crafted for us using primarily Asian floral ingredients, which is also rated as very unfamiliar by our participants. To date we have had no post-experimental complaints or reports from participants alleging any persistent aftereffects from this study. No allergic responses to the fragrances were anticipated and none have been observed or reported.

To date, no adverse events (either minor or serious) have been reported to us at anytime. In order to minimize the potential for such effects, we have used laboratory stressors which are rather benign (public speaking and mental arithmetic). While increased stress levels (via self-report and physiological changes) have been noted among many of the participants following the stress manipulation, such effects have appeared fairly transient. In fact, the need to minimize the impact on subjects may to some extent compromise our ability to view the impact of odor-stress conditioning at any level close to what might be experienced in a real-world setting. For this reason, we are seeking in Year 4 to use additional stressors in order to observe if the magnitude of response will be somewhat greater and less variable among the population. However, we will

only do so if it can be done in a way that ensures the safety and comfort of the participants both during and following the study.

Important to our need to use deception for this study is that subjects *will* consent to some potentially stressful and unpleasant experiences in advance, without knowing exactly the nature of those experiences (which would serve to neutralize the stress value). Of course, we make certain the subject understands on multiple occasions that they can withdraw from the study at any time without penalty.

To ensure safety and prompt reactions in response to participant distress during the experimental procedure, 1) participants will be continuously monitored through video surveillance by the investigator, and 2) heart rate and respiration frequency, which are monitored during the entire experiment, will be visible to the investigator on a computer display outside of the testing chamber.

All subjects receive a formal **debriefing** following the last session, in addition to their ability to ask and have answered any questions regarding the study or their reactions. The debriefing addresses the purposes of the experiment as well as issues such as the possibility of carry-over to real life. Together with the consent form, these documents provide participants with an opportunity to contact us or the Institutional Review Board in case of questions or when experiencing side-effects from participation in our study. As stated earlier, no such reports have been made.

KEY RESEARCH ACCOMPLISHMENTS:

- Observed that a single presentation of the conditioned stimulus (odor) <u>in the absence of the stressor</u> was sufficient to reduce the magnitude of the stress response on a subsequent re-exposure. However, the amplitude of the conditioned response was not very robust, and thus extrapolations to real-world conditioned stress responses must be made cautiously.
- Found reliable differences in the extent to which a conditioned stress response was manifest as a function of personality traits. Individuals high in NA showed less extinction of the conditioned response than did individuals low in NA.

REPORTABLE OUTCOMES:

2 presentations were made at the Association of Chemoreception Sciences Meeting in Sarasota, Florida in April 2004 reporting the results of Study 2 and 3.

Abstracts

C. Maute, M. Gould & P. Dalton (In press) ODOR CONDITIONING AND THE STRESS RESPONSE, Chemical Senses

P. Dalton, C. Maute, F. Naqvi (In press) ODOR PERCEPTION AND JUDGED PROBABILITIES OF HEALTH RISK, Chemical Senses

A manuscript is in preparation reporting the results of these studies

CONCLUSIONS:

Odors that are paired with a stressful situation appear to subsequently elicit a negative response that is not observed to the same degree when only the experimental context is present during conditioning and test phases. This response can be seen in self-reported annoyance to the odor, self-reported stress ratings during odor exposure, and judged, but not objective, performance on a cognitive learning and memory task. Although the response can be extinguished when the odor is re-presented without the stressor, the conclusions from this study are not as firm, as the level of conditioning of the stress response in this study was not very robust. This could be due to the participant sample, or to changes over the past several years in the perception of stress from experimental stimuli when compared with real-world stressors. For this reason, we aim to propose adding to the stress manipulation for the final year of the project when testing the ability of the stressor to be blocked by pre-exposure to the odor under non-stressful conditions. This will allow us to ascertain whether a moderate level of stress can be effectively neutralized. If this proves to be true, we may have an effective way of neutralizing the ability of novel sensory stimuli to become associated with emotional states, such as is experienced in deployment situations. Thus, the paradigm investigated in this project can serve as a useful laboratory-based model system for examining and understanding the persistent symptom constellations found in GWS and other stress-mediated syndromes.

The Gulf War exemplified a trend of increasing threat posed by chemical warfare and biological weapons, accompanied by improved access through media, internet and other resources, to information about the nature and hazard potential of these agents. The combination of actual threat of exposure to dangerous agents and their odors, and the knowledge about the hazard potential and health effects of exposures, introduces a new factor to modern warfare that needs to be acknowledged and understood. This factor is the increased likelihood of a syndrome of health symptoms brought on by potential exposure to probably hazardous odors, their feared effects, and their stress potential. The prospect for GWS –like illness extends beyond the Persian Gulf War, and is likely to intensify.

REFERENCES:

Binder, L. M., Storzbach, D., Kent Anger, W., Campbell, K. A., Rohlman, D. S., & Other Members of the Portland Environmental Hazards Research Center (1999). Subjective cognitive complaints, affective distress, and objective cognitive performance in Persian Gulf War veterans. *Archives of Clinical Neuropsychology, 14,* 531-536.

Bouton, M. E., Barlow, D. H., & Mineka S. (2001) A modern learning theory perspective on the etiology of panic disorder. Psychological Review 108, 4-32.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24,* 385-396.

Dalton, P. (1996). Odor perception and beliefs about risk. *Chemical Senses, 21,* 447-458.

Dalton, P., Gould, M., Girten, B., Stodieck, L. S., & Bateman, T. A. (2003). Preventing annoyance from odors in spaceflight: a method for evaluating the sensory impact of rodent housing. *Journal of Applied Physiology, 95,* 2113-2121.

Dalton, P., Wysocki, C. J., Brody, M. J., & Lawley, H. J. (1997). The influence of cognitive bias on the perceived odor, irritation and health symptoms from chemical exposure. *International Archives of Occupational & Environmental Health, 69,* 407-417.

Dahlgren,A., Akerstedt,T., & Kecklund,G. (2004). Individual differences in the diurnal cortisol response to stress. *Chronobiology International.,* 21(6), 913-922.

Green, B. G., Dalton, P., Cowart, B. J., Shaffer, G., Rankin, K. R., & Higgins, J. (1996). Evaluating the "Labeled Magnitude Scale" for measuring sensations of taste and smell. *Chemical Senses, 21,* 323-334.

Karkow,F.J., Spiandorello,W.P., Godoy,R.F., Pezzi,P., Karkow,A.G., & Faintuch,J. (2004). Subjective versus objective stress in noncritically ill hospitalized and outpatient adult men. *Rev.Hosp.Clin.Fac.Med.Sao Paulo,* 59(4), 161-167.

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test'. A Tool for Investigating Psychobiological Stress Responses in a Laboratory Setting. *Neuropsychobiology, 28,* 76-81.

Lees, P. S. J., Stefaniak, A., Emmett, E. A., & Dalton, P. Exposure assessment for study of olfactory function in workers exposed to styrene in the reinforced-plastic industry. *American Journal of Industrial Medicine, 1,* 1-12 (2004).

McNair, D. M., Lorr, M., & Droppleman, L. F. (1992). *Manual: Profile of Mood States. Revised.* San Diego: Education and Industrial Testing Service.

Rosal,M.C., King,J., Ma,Y., & Reed,G.W. (2004). Stress, social support, and cortisol: inverse associations? *Behavioral Medicine* 30(1), 11-21.

Smeets, M. A., Maute, C. M., & Dalton, P. (2002). Acute sensory irritation from exposure to isopropanol in workers and controls: Objective versus subjective effects. *Annals of Occupational Hygiene,* 359-373.

Van den Bergh, O., Stegen, K., Van Diest, I., Raes, C., Stulens, P., Eelen, P. et al. (1999). Acquisition and extinction of somatic symptoms in response to odours: a pavlovian paradigm relevant to multiple chemical sensitivity. *Occupational and Environmental Medicine, 56,* 295-301.

Watson, D. & Pennebaker, J. W. (1989). Health complaints, stress, and distress: Exploring the central role of negative affectivity. *Psychological Review, 96,* 234-254.

APPENDICES: None